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EXAMINER	
EWOLDT, GERALD R	

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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,788	ZAGHOUANI ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13 and 15-26* is/are pending in the application.

4a) Of the above claim(s) *8-12,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,13,15-19 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments, remarks, and 1.132 declaration of Inventor Zaghouani, filed 12/19/07 are acknowledged.

2. Claims 8-12, 20, and 21 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-5, 7, 13, 15-19, and 22-26 are under examination.

3. Applicant's amended Title has been entered. The Abstract stands objected to because the amended Abstract has not been filed on a separate sheet as is required. See MPEP 608.01(b).

4. In view of Applicant's amendments the previous rejections under the second paragraph of 35 U.S.C. 112, as well as the rejections under the first paragraph of 35 U.S.C. 112 for the introduction of new matter into the claims, have been withdrawn.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5, 7, 13, 15-19, and 22-24 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

As set forth previously, there is insufficient written description to show that Applicant was in possession of a "protein fragment or peptide derived from GAD [now limited to GAD1 or GAD2]", except for GAD65 peptides 524-543 and 206-220.

The claims encompass the use of a genus of any peptides or "derivatives" of GAD. Thus, the claims encompass peptides comprising additions, deletions, mutations, etc., none of which are described in the specification. It is clear that the genus is large, indeed it might be essentially unlimited. Accordingly, one of skill in the art would conclude that the specification fails to disclose a representative number of species, or a common structure and function among the peptides of protein fragments, to describe the claimed genus. See *Eli Lilly*, 119

F.3d 1559, 43 USPQ2d 1398.

Applicant's arguments, filed 12/19/07, have been fully considered but are not found persuasive. Applicant argues that the newly submitted amendments to the claims overcome the rejection.

Applicant's amendment has not actually limited the scope of the claims. Given that with enough additions, deletions, and mutations *any* protein can be "derived" from any other protein, limiting the starting protein to GAD1 (GAD67) or GAD2 (GAD64) does not limit the scope of the claims. Further note that a review of the NCBI database for GAD1 reveals 41 results and 96 related structures. A review of the NCBI database for GAD2 reveals 24 results and 69 related structures. It is unclear which of these GADs are encompassed for use in the claimed method, but it is clear that none of them have been adequately described.

7. Claims 1-5, 7, 13, 15-19, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could effectively function as a method for suspending, preventing or delaying the onset of type I diabetes (IDDM).

As set forth previously, While the mechanism of action for the method of the instant claims is not disclosed, it appears to require inducing tolerance to GAD and altered GAD "derived" peptides. Tolerance-inducing peptide immunotherapy is well known in the immunological arts. In some cases significant results have been demonstrated in in-bred small animal models. However, said results have not been repeated in human trials. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for multiple sclerosis, MS) and Colloral (for rheumatoid arthritis, RA) provided successful results in rodent models (EAE and collagen induced arthritis, respectively).

As set forth above, the references demonstrate that even unsubstituted peptides (peptides that are not APLs) that work in *in vivo* small animal disease models cannot be expected to work in humans. Regarding the even more unpredictable APLs, Anderton (2001), teaches that:

> "This unpredictability [of APLs] led us to argue against the use of antagonist or immune deviating APL in human autoimmune disorders" (page 370).

Indeed, the reference goes on to teach that APL administration to humans can be dangerous and that in at least one case a human trial was suspended due to adverse reactions in a significant number of patients.

Other investigators have discussed additional problems in establishing human tolerance. See, for example, Dong et al. (1999):

> "Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. *Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn*",

emphasis added.

A review of the instant specification shows just a single long example wherein a T cell response to a single insulin B chain peptide (amino acids 9-23) is inhibited in the experimental NOD mouse model of IDDM. First note that the instant claims are drawn to the use of GAD, not insulin, for the suspending, preventing or delaying the onset of IDDM. Thus, the specification offers *no* data in support of the claimed method. Interestingly, the specification discloses, that even regarding the use of an insulin peptide for the suspending, preventing or delaying the onset of IDDM, *the method of the instant claims cannot function as claimed*, emphasis added. For example, at page 28 of the specification, it is disclosed that, "Soluble Ig-INSβ displayed dose dependent delay of diabetes when given at either stage [pre or post IAA conversion]. However, aggregated Ig-INSβ, which induced IL-10 and TGFβ-producing T cells, thus involving sustained endogenous IL-10, was protective against diabetes when given before development of insulitis *but had no effect in predisposed mice positive for IAA*", emphasis added. Further, Examples 7 and 9 teach that neither soluble nor aggregated Ig-INSβ can actually prevent IDDM, but rather can only delay onset under specific conditions.

Additionally, Applicant's subsequent work demonstrates that the method of the instant claims would not be expected to function as claimed. See for example Legge et al. (1998). Therein the authors teach that APLs function as, "T cell antagonists, partial agonists, or super agonists" (page 106). The authors go on to teach that PLP-LR stimulated PLP-1 specific T cells (paragraph spanning page 109 and 110), i.e., the T cells that would be pathogenic in an MS patient. Given that *no* experiments have been performed employing GAD peptides and derivatives thereof, it is just as likely that the method of the instant claims would actually exacerbate disease as treat or prevent it.

A set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory

> requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses *no* data regarding the treatment or prevention of IDDM employing GAD peptides, and the unpredictability of the art, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 12/19/07, have been fully considered but are not found persuasive. Applicant argues that the burden of establishing a non-enabling specification is on the Examiner. After reviewing the references cited by the Examiner Applicant discounts their teachings.

Regarding the *Marketletter* reference, Applicant argues that the Myloral and Colloral trials described therein were not complete failures, but rather, "their tests simply proved them to be no more efficacious than placebos". Applicant further argues that the instant delivery method is 100-fold increased as compared to that of free peptides.

Most skilled artisans would consider treatments "no more efficacious than placebos" to be failures. Regarding the 100-fold increase, said increase, if true, would just as likely provide 100-fold more chance of a negative or harmful response.

Regarding Dong et al., Applicant argues that the reference is "attenuated" from the instant invention.

It is well understood by the skilled artisan that mechanisms of inducing tolerance would likely share some commonality, thus, the reference provides evidence that methods that work in small inbred animal models are not necessarily predictive of results in humans.

Applicant cites newly submitted Baxter et al. in support. Applicant further argues that the Inventor's NOD mouse animal model should be accepted absent evidence to the contrary.

A review of Baxter et al. leads to an article cited therein of Couzin (2003). In that article Couzin teaches of at least two failed attempts at treating human diabetes by inducing tolerance to insulin (both injected and oral). Note that both oral and injected insulin could be used to induce tolerance in the NOD mouse. A third failed trial (that of nicotinamide)

might also be considered relevant to the instant invention as it successfully treated diabetes in mice but was a failure in humans. While Baxter et al. might attempt to dismiss these negative findings the fact remains that there are *no* positive findings in human trial on which to base any optimism. See also the more recent teachings of Harrison (2008) wherein the author bluntly states, "This strategy [the induction of immune tolerance] is therapeutically effective in inbred rodent models but its translation to humans has failed to meet expectations" (Abstract). Accordingly, it appears that the only actual evidence of record supports the position that results of therapies in animal models cannot be used to predict the results of the same therapies in humans.

Finally note that Applicant has not addressed the dangers of administering APL generically, and the *only* remarks Applicant has provided regarding the Inventor's own teachings (Legge et al. (1998)) that the use of APLs is unpredictable and might actually exacerbate disease, are "The fact that at the time the present application was filed it was equally likely that the presently claimed embodiments of the invention would exacerbate disease as treat or prevent it is *per se* unpredictability" (page 12 of the instant remarks). Clearly, Applicant *agrees* that the method of the instant claims is unpredictable and not enabled by the instant specification.

Regarding the Inventor's 1.132 declaration, it appears that the Inventor has recently established some efficacy in the NOD mouse model employing an unidentified "soluble Ig-GAD2". The Inventor's results are noted, however, as set forth above, said results are not enabling for the use of the claimed method for the suspending, preventing, or delaying the onset of IDDM in humans. Further it is unclear if the treatment was capable of actually suspending established disease or rather limited to preventing or delaying disease.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-5, 7, 13, 15-19, and 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/30706 in view of Kaufman et al. (1992).

As set forth previously, WO 98/30706 teaches the treatment of autoimmune disorders, including IDDM, (see particularly pages 10 and 19) employing an engineered fusion protein, e.g., a humanized IgG_{2b} chimeric protein wherein an autoantigen peptide is inserted into the D segment of a CDR3 loop (see particularly Figure 1, page 13, and Example II).

The method differs from the claimed invention only in that it does not teach the use of GAD65 as the autoantigen employed for the treatment of IDDM.

Kaufman et al. teach that GAD65 (which would comprise amino acid residues 206-220 and 524-543), along with insulin, is a well-known IDDM autoantigen (see particularly page 283, column 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of WO 98/30706 for the treatment of IDDM employing the autoantigen of Kaufman et al. One of ordinary skill in the art at the time the invention was made would have been motivated to select GAD65 as the autoantigen for use in the claimed method given the teachings of Kaufman et al. that GAD65 was one of the few known IDDM autoantigens at the time of the invention. Regarding the timing of administration of the Ig-fusion protein set forth in claims such as 3, 16, 17, etc., said timing would comprise only routine optimization which would fall well within the purview of one of skill in the art at the time of the invention.

Applicant's arguments, filed 12/19/07, have been fully considered but are not found persuasive. Applicant argues that their would have been no expectation of success in achieving beneficial results. Specifically, Applicant argues that in WO 98/30706 administration of individual PLP peptides alone induced or agonized disease whereas the administration of both an unaltered and altered PLP peptide simultaneously was required to inhibit disease.

In view of the teachings of WO 98/30706 the ordinarily skilled artisan would likely have developed a treatment employing a combination of unaltered and altered GAD peptides to avoid the problems that might have occurred due to the administration of individual peptides. Employing this strategy the ordinarily skilled artisan would have had every expectation of success in developing an effective treatment.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-5, 7, 13, 15-19, and 22-26 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/290,070. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '070 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 11-5, 7, 13, 15-19, and 22-26 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/425,084. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '084 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The rejection over the claims of U.S. Application No. 10/510,411 has been withdrawn due to the amending the claims in that application.

Applicant defers a response regarding the remaining rejections until the finding of allowable claims.

13. No claim is allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen

O'Hara, Ph.D. can be reached on (571) 272-0878.

16. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197

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